THE CLEAVAGE OF SULFONAMIDES IN ACIDIC REDUCING MEDIA

BY

HENRY CHARLES GELLER

B.A., University of California, Los Angeles, 1944
B.A., The Rice Institute, 1948
A.M., University of Illinois, 1949

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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Introduction

The cleavage of sulfonamides has been a topic of considerable interest to organic chemists for a two-fold reason. On the one hand the widely-used Hinsberg method for the separation of primary, secondary, and tertiary amines requires the formation of sulfonamides, while on the other hand the sulfonyl radical is commonly used as a protective group for amines *via* the formation of sulfonamides. In both instances it is usually necessary to recover the amine by cleaving the sulfonamide.

The most common method of cleaving sulfonamides, the hydrolysis with 25% hydrochloric acid or strong alkali, proceeds slowly and in poor yield. Reductive cleavages using hydriodic acid[1] have been employed in several significant cases but the sealed-vessel reaction conditions have limited the utility of the reaction. Hydrogen bromide in glacial acetic acid has been used successfully as a reductive cleavage agent.[2] A general method for splitting sulfonamides by the use of 48% hydrobromic acid and phenol as a bromine acceptor has been developed in this Laboratory.[3]

The purpose of this investigation has been to elucidate the course of the hydrobromic acid and phenol cleavage and to study the cleavage of sulfonamides by aqueous hydrobromic acid in other reducing media and by other reducing agents.

Discussion of Results

Benzene-, *p*-toluene, mesitylene-, and methanesulfonanilides were cleaved in thirty minutes to one hour with constant-boiling hydrobromic acid (48%, b.p. 124-126°) and phenol to give aniline in good yield; *p*-bromophenol, but no mercaptan or disulfide, was formed. When phenol was absent disulfides

were obtained, diphenyldisulfide in 32% and di-*p*-tolyldisulfide in 41% yield. When phenol was reduced in amount, diphenyldisulfide formed in 11% yield. The cleavage of β-naphthalenesulfonanilide with 48% hydrobromic acid and phenol gave, in addition to aniline in 79% yield, a hydroxyphenyl β-naphthyl sulfide in 50% yield indicating that thioalkylation of the active phenolic nucleus is a faster reaction than disulfide formation.

The substitution of strong inorganic reducing agents for the phenol as bromine acceptors led to the isolation of mercaptans and disulfides. *p*-Toluenesulfonanilide reacted with 48% hydrobromic acid and stannous chloride yielding aniline (50%), *p*-thiocresol (16%), and di-*p*-tolyldisulfide (8%). Stannous chloride with 25% hydrochloric acid produced little cleavage of *p*-toluenesulfonanilide during the one hour reaction period. Cuprous bromide formed a complex with the concentrated hydrobromic acid and failed to prevent bromination of the aromatic nucleus of the amine; benzenesulfonanilide yielded *p*-bromo-, 2,4-dibromo-, and 2,4,6-tribromoaniline, as well as diphenyldisulfide. Hydrazine and 48% hydrobromic acid reductively cleaved benzene- and *p*-toluenesulfonanilides but hydrazine alone had no effect on benzenesulfonanilide.

The postulated formation of a sulfenyl bromide[4] (RSBr) as an intermediate most adequately accounts for the products from the hydrobromic acid reduction of sulfonamides, although a free mercaptide radical (RS·) intermediate would suffice.

A reaction of orthophosphorous acid with sulfonanilides proved to be a reductive cleavage. Benzenesulfonanilide, when heated for forty minutes at 190-195° with orthophosphorous acid, gave aniline in 51% yield and a small amount of thiophenol (4%); under the same conditions aniline in 53% yield was obtained from mesitylenesulfonanilide and the evolution of hydrogen sulfide was observed.

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VITA

The author was born on November 21, 1923, in Houston, Texas, where he received his pre-college education. After graduating from San Jacinto High School in 1940, he matriculated at The Rice Institute in Houston. In 1943 he was called to active duty with the Army Air Forces, where he served until 1946. During a portion of this period, under the auspices of the A.A.F., he studied at the University of California at Los Angeles where he received a Bachelor of Arts degree in Physics-Meteorology. After serving in the American and India-Burma theaters, he was discharged from the army and re-entered The Rice Institute. He was graduated from Rice in June, 1948, receiving the degree of Bachelor of Arts with Honors in Chemistry. In June, 1949, he received a Master of Arts degree in Chemistry from the University of Illinois. While studying for his doctorate there, he held University Fellowships during the academic years 1948-49 and 1949-50 and was a Minnesota Mining and Manufacturing Company Fellow in the academic year 1950-51.